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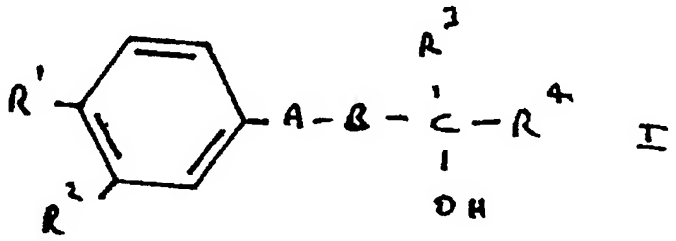
(54) Compounds for the treatment of urinary incontinence

(57) Compounds of formula I



wherein:

(a) one of R^1 and R^2 represents (1-4C)alkyl, {(1-4C)alkyl}{(1-4C)alkanoyl}amino, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl, and the other of R1 and R2 represents hydrogen or (1-4C)alkyl, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl;

(b) -A-B- is selected from NHCO, OCH_2, $NHCH_2$, trans- vinylene and ethynylene

(c) R^3 and R^4 are independently (1-3C)alkyl substituted by atoms selected from fluoro and chloro or R^3 and R^4, together with the carbon atom to which they are attached, form a 3 to 5 membered cycloalkyl ring optionally substituted with fluorine atoms.

(d) a pharmaceutically acceptable in vivo ester or compound I.

The compounds are potassium channel openers and are useful for the treatment of urinary incontinenece.

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The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1990.

THERAPEUTIC COMPOUNDS

This invention relates to the use of certain compounds in the treatment of bladder instability in mammals such as man and as potassium channel openers.

It is known that bladder tissue is excitable and that urinary incontinence can be caused by uncontrolled or unstable bladder contractions.

It has now been found that certain compounds (some of which are disclosed in EP-A1-2892 as anti-androgens) are unexpectedly capable of relaxing bladder smooth muscle, thus preventing or ameliorating uncontrolled or unstable bladder contractions. Hence, the compounds may be useful for the treatment of urge incontinence, which includes for example detrusor instability, which may result from cystitis, urethritis, tumors, stones, diverticuli or outflow obstruction; and detrusor hyperreflexia, which may result from stroke, dementia, Parkinsons, suprasacral spinalcord injury or suprasacral spinalcord disease.

This invention provides the use of a compound of formula I (formula set out, together with other formulae referred to by Roman numerals, at the end of this specification), wherein:

one of R^1 and R^2 represents (1-4C)alkyl, {(1-4C)alkyl}{(1-4C)alkanoyl}amino, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl, and the other of R1 and R2 represents hydrogen or (1-4C)alkyl, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl;

A-B is selected from NHCO, OCH_2, $NHCH_2$, trans-vinylene and ethynylene;

R^3 and R^4 are independently (1-3C)alkyl substituted by from 0 to 2k+1 atoms selected from fluoro and chloro wherein k is the number of carbon atoms in the said (1-3C)alkyl, provided that R^3 and R^4 are not both methyl; or

R^3 and R^4, together with the carbon atom to which they are attached, form a 3-5 membered cycloalkyl ring optionally substituted by from 0 to 2m-2 fluorine atoms wherein m is the number of carbon atoms in said ring;
or a pharmaceutically acceptable in vivo hydrolyzable ester of said compound of formula I;
or a pharmaceutically acceptable salt of said compound or said ester in the manufacture of a medicament for the treatment of urinary incontinence.

The invention further provides a method for the treatment of urinary incontinence, comprising administering to a mammal (including man) in need of such treatment an effective amount of an amide of formula I as defined above, or a pharmaceutically acceptable in vivo hydrolyzable ester of said compound of formula I or a pharmaceutically acceptable salt of said compound or said ester.

The invention also provides those compounds of formula I, and the in vivo hydrolysable esters and pharmaceutically acceptable salts thereof that are novel.

The invention further provides a pharmaceutical composition comprising a novel compound of formula I as defined above, or a pharmaceutically acceptable in vivo hydrolyzable ester of said compound of formula I or a pharmaceutically acceptable salt of said compound or said ester, and a pharmaceutically acceptable diluent or carrier.

In this specification the terms "alkyl" and "alkoxy" include both straight and branched chain radicals, but it is to be understood that references to individual radicals such as "propyl" or "propoxy" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" or "isopropoxy" being referred to specifically.

The term "halo" is inclusive of fluoro, chloro, bromo, and iodo unless noted otherwise.

It will be appreciated by those skilled in the art that certain compounds of formula I contain an asymmetrically substituted carbon atom, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit

polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of urinary incontinence, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the treatment of urinary incontinence by the standard tests described hereinafter.

The use of compounds in the form of the (S)-enantiomer is preferred.

Particular values for a substituent represented by R^1 are hydrogen, methyl, ethylacetylamino, methanesulphonyl, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, cyclohexylsulphonyl, phenylthio and benzylsulphonyl.

Particular values for a substituent represented by R^2 are hydrogen, ethylacetylamino, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl and phenylthio.

Examples of values for R^1 and R^2 together with the phenyl group to which they are attached are 4-methylphenyl, 4-ethylacetylphenyl, 3-chloro-4-methanesulphonylphenyl, 4-nitrophenyl, 3-phenylthio-4-nitrophenyl, 3-chloro-4-nitrophenyl, 3-trifluoromethyl-4-nitrophenyl, 4-cyanophenyl, 3,4-dicyanophenyl, 3-chloro-4-cyanophenyl, 3-trifluoromethyl-4-cyanophenyl, 3-cyanophenyl, 4-chloro-3-ethylacetylaminophenyl, 4-bromo-3-trifluoromethylphenyl, 4-cyclohexylsulphonylphenyl, 3,4-dichlorophenyl and 4-benzylsulphonylphenyl.

Preferably A-B represents NHCO, OCH_2, trans-vinylene or ethynylene. Most preferably it represents NHCO, trans-vinylene or ethynylene.

Preferably either R^3 and R^4 both represent difluoromethyl, or R^4 represents trifluoromethyl and R^3 represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl. More preferably R^4 represents trifluoromethyl and R^3 represents methyl.

A compound of formula I can be made by processes which include processes known in the chemical arts for the production of structurally analogous compounds. In respect of novel compounds of formula I, such processes are provided as further features of the invention and are illustrated by the following procedures in which the meanings of generic radicals are as given above unless otherwise qualified. Such a process can be effected, generally,

(a) by deprotecting a protected compound of formula II wherein "Pg" is a suitable alcohol protecting group, such as for example a benzyl group or a silyl protecting group; Examples of suitable reagents for deprotecting an amide of formula II when Pg is benzyl are (1) hydrogen in the presence of palladium-on-carbon catalyst, i.e. hydrogenolysis; or (2) hydrogen bromide or iodide; and when PG is a silyl protecting group are (1) tetrabutylammonium fluoride; or (2) aqueous hydrofluoric acid. The reaction can be conducted in a suitable solvent such as ethanol, methanol, acetonitrile, or dimethylsulfoxide and may conveniently be performed at a temperature in the range of -40 to 100 °C.

(b) for a compound of formula I in which A-B is NHCO, by coupling an aniline of formula III with an acid of formula IV. The reaction can be conducted in a suitable solvent and in the presence of a suitable coupling reagent. Suitable coupling reagents generally known in the the art as standard peptide coupling reagents can be employed, for example thionyl chloride, carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran, and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40 °C;

(c) for a compound of formula I in which A-B is ethynylene, by reacting a corresponding alkyne of formula V with a base such as lithium diisopropylamide (LDA), n-butyllithium or tert-butyllithium, followed by treatment with a ketone of formula R^3-CO-R^4. The reaction may conveniently be performed at a temperature in the range of -100 to -40 °C preferrably at a temperature in the range of -70 to -40 °C and

in a solvent such as tetrahydrofuran (THF), diethyl ether, or 1,2-dimethoxyethane (DME).

(d) for a compound of formula I in which A-B is trans-vinylene, by reducing a corresponding compound of formula I in which A-B is ethynylene with a suitable reducing agent, for example lithium aluminum hydride or sodium bis(methoxyethoxy)aluminium hydride. The reaction can be conducted in a suitable solvent such as THF or diethyl ether, and at a temperature in the range of 0 to 50 °C.

(e) for a compound of formula I in which A-B is tran-vinylene, by dehydration of a diol of formula VI in the presence of an acid catalyst (for example p-toluenesulfonic acid), neat or with a solvent such as toluene or dichloromethane, or a strong base (for example sodium hydride) in a solvent such as tetrahydrofuran and at a temperature in the range of 0 to 200 °C preferably a temperature in the range of 20 to 100 °C.

(f) for a compound of formula I in which A-B is trans-vinylene, by base catalyzed opening of an epoxide of formula VII. The opening may be carried out in a suitable organic solvent such as for example, ethers, alcohols, or toluene; ethers such as tetrahydrofuran are preferred. Suitable bases include for example sodium hydroxide, sodium methoxide, potassium tert-butoxide or sodium hydride. A basic aqueous solution may conveniently be employed. A preferred base is aqueous sodium hydroxide. The opening may be carried out at a temperature in the range of -50 °C to 100 °C, preferably at a temperature in the range of 0 to 50 °C, such as for example room temperature.

(g) for a compound of formula I in which A-B is $NHCH_2$, by reducing a corresponding compound of formula I in which A-B is NHCO, with a suitable reducing agent such as lithium aluminum hydride or borane. The reaction can conveniently be carried out at a temperature in the range of 0 °C to reflux, in solvents such as for example diethyl ether, THF, or DME.

(h) for a compound of formula I in which A-B is OCH_2, by reacting an ethylene oxide of formula VIII with a corresponding compound of formula IX (wherein J is, correspondingly, oxygen), in the presence of a base such as for example sodium hydride. The reaction

can be conducted at reflux in a solvent such as methylene dichloride.

If not commercially available, the necessary starting materials for the procedures such as that described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the examples.

In general, a compound of formula II in which A-B is OCH_2 or $NHCH_2$ may be made by treating a corresponding compound of formula IX wherein J is oxygen or NH with a corresponding compound of formula X (wherein Pr is a protective group such as silyl and X is a suitable leaving group such as for example mesylate or triflate), in the presence of a base such as an alkali metal hydride (e.g., sodium hydride), in a solvent such as THF, DMF, DMSO, or DMPU, and at a temperature of about 20 °C to about reflux. A compound of formulae II, wherein A-B is NHCO, may be made in a manner analogous to that described in procedure (b) above; that is, by coupling a corresponding aniline with a corresponding acid. The protected acid may be made by a conventional procedure, for example by (i) esterifying an acid of formula IV by means of a conventional esterification procedure such as reaction with a lower alcohol (e.g., methanol) in the presence of an acid catalyst (for example sulfuric acid); (ii) reaction of the ester thus formed with an agent which provides the protecting group Pg, such as benzyl chloride (to provide a benzyl protecting group) or any of the conventional silylating agents known and used for such purpose (such as 2-trimethylsilylethoxymethyl chloride, SEM, in the presence of a suitable base such as sodium hydroxide or triethylamine optionally in the presence of a catalyst such as DMAP); and (iii) cleavage of the ester group under mild alkaline conditions (i.e., employing a base such as potassium carbonate) to yield the desired protected acid.

A compound of formula V may be made by reacting a corresponding compound of formula XI, wherein L is bromo or iodo, with trimethylsilylacetylene in the presence of a catalyst such as a combination of bis(triphenylphosphine)palladium dichloride and

copper(I) iodide in diethylamine or triethylamine, followed by treatment with a base (for example, an alkali metal hydroxide such as sodium or lithium hydroxide) in a lower alcohol as solvent to effect removal of the trimethylsilyl group.

A compound of formula VIII may be made by treating a corresponding ketone having the formula R^3-CO-R^4 with the ylide derived from the reaction of a trimethylsulfonium salt (such as trimethylsulfonium iodide) with a base (such as an alkali metal hydroxide). The reaction may be conducted in a one-pot process employing a solvent such as dichloromethane.

A compound of formula IX, wherein J is oxy, may be made by diazotizing a corresponding aniline of formula XI, wherein L is amino, as previously discussed, and heating in dilute sulfuric acid to form the corresponding phenol.

A compound of formula X, wherein X is mesylate, may be made by (1) esterifying an acid of formula IV; (2) protecting the alcohol group, by treating with for example trimethylsilyl chloride in a solvent such as dichloromethane and at a temperature of from about -78 to about 25 °C; (3) treating the protected compound thus obtained with a suitable reducing agent such as lithium aluminum hydride in a solvent such as diethyl ether or THF and at a temperature of about 0 to about 25 °C, thereby reducing the carbonyl group to methylene; followed by (4) treating the reduced product with trifluoromethylsulfonic anhydride in the presence of a base such as triethylamine, in a solvent such as dichloromethane, and at a temperature of about -78 °C to about 25 °C.

An epoxide of formula VII may be prepared from a diol of formula VI using a suitable dehydrating agent, for example bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulphur. A diol of formula VI may be prepared from a compound of formula I, wherein A-B is CHCO, by reduction. The reduction may be carried out using a suitable reducing agent, for example a hydride, such as sodium borohydride.

A compound of formula I, wherein A-B is CHCO, may be prepared from a compound of formula XI, wherein L is methyl, by deprotonation and treatment with an amide of formula XII, in which R^6

and R^7 are each independently lower alkyl, or in which R^6 and R^7 when taken together with the atoms to which they are attached form a 5-7 membered ring. The deprotonation of the toluene may be carried out with a suitable base, for example lithium diisopropyl amide. The reaction may be carried out in a suitable organic solvent, for example, an ether such as tetrahydrofuran. The reaction may be carried out at a suitable temperature, for example a temperature in the range of -78 °C to 100 °C.

An amide of formula XII may be prepared from an acid of formula IV, or a reactive derivative thereof, by reaction with the corresponding amine.

In cases where compounds of formula I are sufficiently basic or acidic to form stable acid or basic salts, administration of the compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described following. Examples of suitable pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiologically acceptable anion, for example, tosylate, methanesulfonate, acetate, tartrate, citrate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed such as sulfate, nitrate, and hydrochloride.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound of formula I (or its ester) with a suitable acid affording a physiologically acceptable anion. It is also possible with most compounds of the invention to make a corresponding alkali metal (e.g., sodium, potassium, or lithium) or alkaline earth metal (e.g., calcium) salt by treating an amide of formula I (and in some cases the ester) with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (e.g. the ethoxide or methoxide in aqueous medium followed by conventional purification techniques.

In vivo hydrolyzable esters of compounds of the invention may be made by coupling with a pharmaceutically acceptable carboxylic acid or an activated derivative thereof. For example, the coupling

may be carried out by treating a parent amide of formula I with an appropriate acid chloride (for example, acetyl chloride, propionyl chloride, or benzoyl chloride) or acid anhydride (for example, acetic anhydride, propionic anhydride, or benzoic anhydride) in the presence of a suitable base such as triethylamine. Those skilled in the art will appreciate that other suitable carboxylic acids (including their activated derivatives) for the formation of in vivo hydrolyzable esters are known to the art and these are also intended to be included within the scope of the invention. Catalysts such as 4-dimethylaminopyridine may also be usefully employed.

When used to treat urinary incontinence, a compound of formula I is generally administered as an appropriate pharmaceutical composition which comprises a compound of formula I as defined hereinbefore together with a pharmaceutically acceptable diluent or carrier, the composition being adapted for the particular route of administration chosen. Such compositions are provided as a further feature of the invention.

The compositions may be obtained employing conventional procedures and excipients and binders and may be in a variety of dosage forms. For example, they may be in the form of tablets, capsules, solutions or suspensions for oral administration; in the form of suppositories for rectal administration; in the form of sterile solutions or suspensions for administration by intravenous, intravesicular, subcutaneous or intramuscular injection or infusion; or in the form of a patch for transdermal administration.

Treatment using a compound according to the invention may be remedial or therapeutic as by administering a compound following the onset or development of urinary incontinence in a patient. Treatment may also be prophylactic or prospective by administering a compound in anticipation that urinary incontinence may develop, for example in a patient who has suffered from incontinence in the past.

According to a further aspect, the invention provides the use of a compound of formula I, as defined hereinabove, in the manufacture of a medicament for the treatment of urinary incontinence.

It has also unexpectedly been found that compounds according to the invention are potassium channel openers. It is known that by

functioning to open potassium channels, potassium channel opening compounds may thereby function to relax smooth muscle.

Because compounds according to the invention function to open cell potassium channels, they may also be useful as therapeutic agents in the treatment of other conditions or diseases in which the action of a therapeutic agent which opens potassium channels is desired or is known to provide amelioration. Such conditions or diseases include hypertension, asthma, peripheral vascular disease, right heart failure, congestive heart failure, angina, ischemic heart disease, cerebrovascular disease, renal cholic, disorders associated with kidney stones, irritable bowel syndrome, male pattern baldness, premature labor, and peptic ulcers.

According to another aspect therefore, the invention provides the use of a compound of formula I, or an in vivo hydrolysable ester thereof or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease or condition in which the action of a potassium channel opener is required.

The dose of compound of formula I which is administered will necessarily be varied according to principles well known in the art taking account of the route of administration, the severity of the incontinence condition, and the size and age of the patient. In general, a compound of formula I will be administered to a warm blooded animal (such as man) so that an effective dose is received, generally a daily dose of above 0.005, for example in the range of about 0.01 to about 10 mg/kg body weight.

It will be apparent to those skilled in the art that a compound of formula I may be co-administered with other therapeutic or prophylactic agents and/or medicaments that are not medically incompatible therewith. Compounds within the scope of the invention have not been found show any indication of untoward side-effects in laboratory test animals at several multiples of the minimum effective dose.

The actions of compounds of formula I as smooth muscle relaxants useful as therapeutic agents for the treatment of urinary incontinence through their action to open potassium channels and

hyperopolarize the membrane electrical potential in bladder detrusor smooth muscle may be shown using suitably designed in vitro tests, such as the one described following. Compounds according to the invention typically exhibit an IC_{50} on the order of 30 micromolar or less in the test. "IC_{50}" is a well understood term and means the concentration of test compound which causes a 50% decrease in the in vitro contraction of the bladder tissue described in the following test.

Male albino Hartley guinea pigs (450-500g) are sacrificed by carbon dioxide induced asphyxiation and quickly exsanguinated. The lower abdominal cavity is opened and the urinary bladder isolated. The bladder is cleaned of surrounding connective and adipose tissue, and the portion above the ureteral orifices is removed and washed in Krebs-Henseleit buffer solution of the following composition (in mM): NaCl 118.0, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25.0 and d-glucose 11.1. The solution is warmed to 37°C and gassed with 95% O_2 and 5% CO_2. With vigorous bubbling, the solution should have a pH value close to 7.4.

The dome of the washed bladder is cut off and discarded; the remaining bladder is placed on a gauze in a Petri dish containing the buffer solution. A mid-ventral longitudinal cut is made with scissors to open the bladder. The strips cut from the dome and the base edge are discarded. The remaining detrusor mid-section is cut into two horizontal strips with an approximate width of 2.0 mm. These two strips are further bisected at the mid-dorsal section, creating four strip of similar dimensions. Each strip thus contains both dorsal and ventral portions of the bladder.

The two ends of each individual strip are tied to a glass support rod and a force-displacement transducer (Grass model FT03), respectively, with 4-0 black braided silk suture.

The transducers are connected to a polygraph (Grass model 7E), which is calibrated at 5 mV/cm and the calibration checked for linearity with weights of 5 and 0.5 grams. The analog electrical output signals from the polygraph are digitized by a Modular Instrument Micro 5000 signal processing system using Biowindow Data Acquisition Software, which is run under the Microsoft OS/2 operating

system with an IBM-compatible PC.

The detrusor strips on the glass rod are secured in 20 ml tissue baths and allowed to equilibrate under a preload tension of 2 grams. During the following 45 to 60 min equilibration period, the tissue is washed with fresh buffer solution at 15 min interval, with the tension adjusted, if necessary, to 2 grams prior to washing. After the equilibration period, a priming dose of 15 mM KCl (total concentration in the bath) is applied. The tissue is washed after 10 min and washed twice more at 15 min intervals with tension adjusted to 2 grams before each washing.

When the tissue relaxes to a steady state after the final washing, 15 mM KCl is again applied. Once the myogenic activity of the tissue reaches a steady state, the baseline data are acquired through the Biowindows Data Acquisition System by averaging 5 min of the myogenic data sampled at 32 Hz. Once the baseline is acquired, the experimental compounds are dosed in a cumulative manner in half log unit increments. The contact time for each dose is 10 min with the final 5 min being the period of time that the dose response data are acquired. If 30 μM of the test compound does not abolished the detrusor mechanical activity, then 30 μM cromakalim, a putative potassium channel opener, is dosed to establish a maximum response. The effect of the compound at each dose is expressed as % of the maximum inhibitory response, which is further normalized with respect to the corresponding effect of the compound vehicle control. The normalized response is then used to derive the IC_{50} of the relaxant activity of the compound through the application of Marquardt's nonlinear iterative curve fitting technique to a standard dose-response function.

The ability of compounds according to the invention to open potassium channels in detrusor smooth muscle can be further demonstrated by a second in vitro test.

This second in vitro test is similar to the one described above with regard to tissue preparation and data acquisition. However, the following exceptions are noted. In this second test, the contraction of the detrusor strips during priming and after the equilibration period is achieved with 80 mM instead of 15 mM KCl

(total concentration in the bath). A sustained tension in the tissue is evident after this high KCl stimulation, because voltage-sensitive calcium channels have been rendered open to permit an influx of calcium into the cells and the development of tonic tension. This tension is totally abolished with 300 μM of papaverine, which is thereby used to establish the maximum response in this test.

Typical calcium channel blockers like nifedipine, nimodipine, isradipine, and verapamil are able to relax and reduce the myogenic activity of guinea pig detrusor strips in both tests by virtue of their blocking action on calcium channels. However, all of the aforementioned calcium channel blockers are more potent in the second test when 80 mM KCl is used, than in the first test where 15 mM KCl is used. In contrast, while the putative potassium channel opener cromakalim has a potent relaxant activity in the first test with an IC_{50} in the range of 0.6 to 0.9 μM, it demonstrates insignificant relaxant activity in the second test at concentrations as high as 30 μM. Thus, the profile of a higher relaxant activity in the first test than in the second of compounds according to the invention indicates that the compounds are functioning as potassium channel openers.

The ability of the compounds according to the invention to act as potassium channel openers on bladder tissue may be further demonstrated by a standard test which measures the effect of test compounds on the rate of efflux of rubidium from the tissue.

For example, the compound 3-chloro-4-cyanophenyl-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide has been found to give an IC_{50} of 3.8 in the above test. Other compounds of formula I which have been tested and found to give an IC_{50} of 30 μM or less include those indicated in the Table below.

TABLE

Example	R^1	R^2	R^3	R4	A-B
1	NO_2	H	CF_3	CH_3	NHCO
2	CH3SO2	Cl	"	"	"
3.	Cl	$(C_2H_5)CH_3CONH$	"	"	"
4.	NO^2	phenylthio	"	"	"
5.	"	CF_3	"	"	"
6.	CN	CN	"	"	"
7.	Br	CF_3	"	"	"
8.	NO^2	"	"	"	"
9.	NO2	H	"	"	OCH_2
10.	CN	H	"	"	NHCO
11.	cyclohexylSO_2	H	"	"	"
12.	Cl	Cl	"	"	"
13.	$(C_2H_5)CH_3CONH$	H	"	"	"
14.	$BzSO_2$	H	"	"	"
15.	NO_2	CF_3	CF_2H	CH_3	"
16.	CN	"	"	"	"
17.	H	CN	CF_3	CH_3	"
18.	NO_2	CF_3	"	C_2H_5	"
19.	CN	"	"	CH_3	"
20.	Cl	NO_2	"	"	"

Bz = benzyl

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

Example 1.

The following illustrate representative pharmaceutical dosage forms containing a compound of formula I (hereafter referred to as "compound X"), for therapeutic or prophylactic use in humans:

(a) Tablet

	mg/tablet
Compound X	50.0
Mannitol, USP	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Hydroxypropylmethylcellulose (HPMC), USP	2.25
Magnesium stearate	3.0

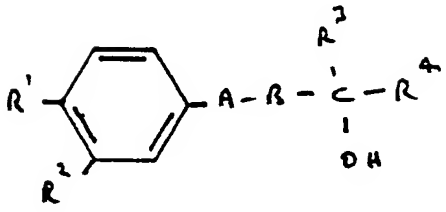
(b) Capsule

Compound X	10.0
Mannitol, USP	488.5
Croscarmellose sodium	15.0
Magnesium stearate	1.5

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

OP09323 11MAY93
MAH/MEB

CHEMICAL FORMULAE



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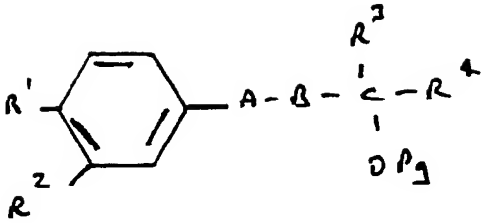

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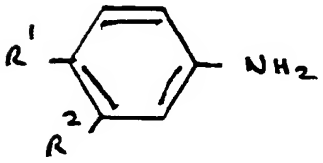

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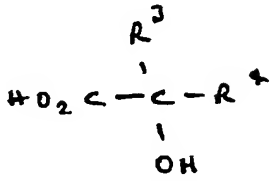

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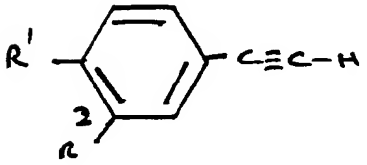

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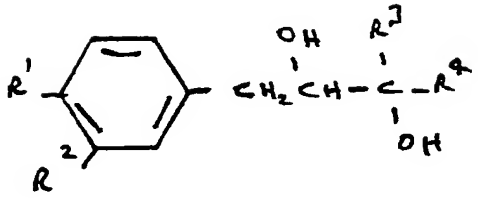

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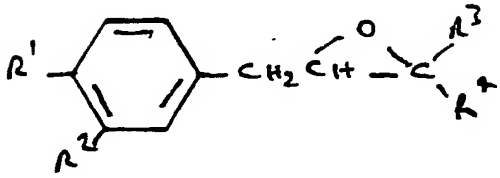
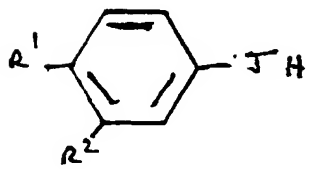


VII

VIII



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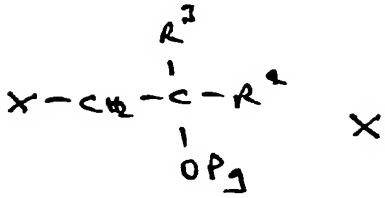

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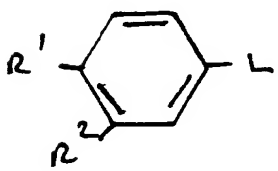

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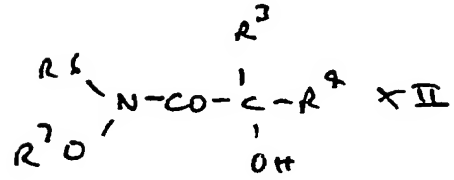
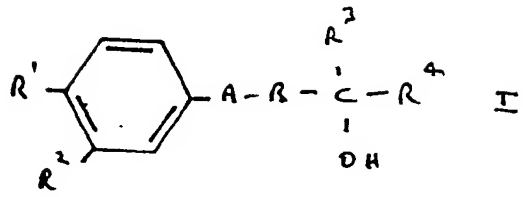


XII

Claims.

1. The use of a compound of formula I



I

wherein:

one of R^1 and R^2 represents (1-4C)alkyl, {(1-4C)alkyl}{(1-4C)alkanoyl}amino, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl, and the other of R1 and R2 represents hydrogen or (1-4C)alkyl, (1-4C)alkylsulphonyl, nitro, cyano, halo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, (5-6C)cycloalkylsulphonyl, phenylthio or aryl(1-3C)alkylsulphonyl, provided that when R^1 is cyano, R^2 is not phenylthio;

A-B is selected from NHCO, OCH_2, $NHCH_2$, trans-vinylene and ethynylene;

R^3 and R^4 are independently (1-3C)alkyl substituted by from 0 to 2k+1 atoms selected from fluoro and chloro wherein k is the number of carbon atoms in the said (1-3C)alkyl, provided that R^3 and R^4 are not both methyl; or

R^3 and R^4, together with the carbon atom to which they are attached, form a 3-5 membered cycloalkyl ring optionally substituted by from 0 to 2m-2 fluorine atoms wherein m is the number of carbon atoms in said ring;

or a pharmaceutically acceptable in vivo hydrolyzable ester of said compound of formula I;

or a pharmaceutically acceptable salt of said compound or said ester in the manufacture of a medicament for the treatment of urinary incontinence.

2. Use as claimed in claim 1, in which R^1 is hydrogen, methyl, ethylacetylamino, methanesulphonyl, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethylsulphonyl, cyclohexylsulphonyl, phenylthio or benzylsulphonyl.

3. Use as claimed in claim 1, in which R^2 is hydrogen, ethylacetylamino, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl or phenylthio.

4. Use as claimed in any one of claims 1 to 3, in which R^1 and R^2 together with the phenyl group to which they are attached are 4-methylphenyl, 4-ethylacetylaminophenyl, 3-chloro-4-methanesulphonyl-phenyl, 4-nitrophenyl, 3-phenylthio-4-nitrophenyl, 3-chloro-4-nitro-phenyl, 3-trifluoromethyl-4-nitrophenyl, 4-cyanophenyl, 3,4-dicyano-phenyl, 3-chloro-4-cyanophenyl, 3-trifluoromethyl-4-cyanophenyl, 3-cyanophenyl, 4-chloro-3-ethylacetylaminophenyl, 4-bromo-3-trifluoro-methylphenyl, 4-cyclohexylsulphonylphenyl, 3,4-dichlorophenyl or 4-benzylsulphonylphenyl.

5. Use as claimed in any one of claims 1 to 4, in which A-B represents NHCO, OCH_2, trans-vinylene or ethynylene.

6. Use as claimed in claim 5, in which A-B represents NHCO, trans-vinylene or ethynylene.

7. Use as claimed in any one of claims 1 to 6, in which either R^3 and R^4 both represent difluoromethyl, or R^4 represents trifluoromethyl and R^3 represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl.

8. Use as claimed in claim 7, in which R^4 represents trifluoromethyl and R^3 represents methyl.

9. Use as claimed in any one of claims 1 to 8, in which the compound of formula I is in the form of the (S)-enantiomer.

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Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report) -19-

Application number
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Relevant Technical Fields

(i) UK Cl (Ed.M) A5B (BHA; BJA)

(ii) Int Cl (Ed.5) A61K (31/085, 31/165, 31/135, 31/275)

Search Examiner
Dr C L DAVIES

Date of completion of Search
18 AUGUST 1994

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ON-LINE DATABASES - CAS-ONLINE

Documents considered relevant following a search in respect of Claims :-
1 TO 9

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
A	GB 2102287 A (SCHERING AG) see Example IV page 4	

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).